

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PG3612/PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/ 10000	International filing date (day/month/year) 16/12/1999	(Earliest) Priority Date (day/month/year) 18/12/1998
Applicant GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.

☐ the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International search was carried out on the basis of the sequence listing :

☐ contained in the International application in written form.

☐ filed together with the International application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 20
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 201 121 A (FARBWERKE HOECHST AG) 5 August 1970 (1970-08-05) claims 1,4,5,7; examples	1, 16, 22-25
A	US 4 105 602 A (R. L. COLESCOTT ET AL.) 8 August 1978 (1978-08-08) column 2, line 26 - line 37 columns 3 and 4, bottom of page, coupling reaction; columns 5 and 6, top of page, coupling reaction	26-28
A	WO 98 54207 A (CELLTECH THERAPEUTICS LTD.) 3 December 1998 (1998-12-03) cited in the application	
A	WO 97 03094 A (BIOGEN, INC.) 30 January 1997 (1997-01-30) cited in the application	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9853817 A	03-12-1998	AU 7703198 A	30-12-1998
WO 9853814 A	03-12-1998	NONE	
WO 9853818 A	03-12-1998	AU 7703298 A	30-12-1998
GB 1201121 A	05-08-1970	CH 496668 A	30-09-1970
		DE 1593858 A	29-10-1970
		DE 1643327 A	27-05-1971
		NL 6802947 A	03-09-1968
		US 3538070 A	03-11-1970
US 4105602 A	08-08-1978	NONE	
WO 9854207 A	03-12-1998	AU 7667498 A	30-12-1998
		EP 0984981 A	15-03-2000
WO 9703094 A	30-01-1997	AU 716276 B	24-02-2000
		AU 6489496 A	10-02-1997
		BG 102241 A	30-12-1998
		BR 9609782 A	09-03-1999
		CA 2226868 A	30-01-1997
		CN 1193325 A	16-09-1998
		CZ 9800052 A	15-04-1998
		EP 0842196 A	20-05-1998
		FI 980033 A	05-03-1998
		HU 9802202 A	28-01-1999
		JP 11511124 T	28-09-1999
		NO 980097 A	11-03-1998
		PL 324491 A	25-05-1998
		SK 3798 A	08-07-1998

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REC'D 19 DEC 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15



Applicant's or agent's file reference PG3612/PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/10000	International filing date (day/month/year) 16/12/1999	Priority date (day/month/year) 18/12/1998
International Patent Classification (IPC) or national classification and IPC C07D211/58		
Applicant GLAXO GROUP LIMITED et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 7 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 23/06/2000	Date of completion of this report 15.12.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fanni, S Telephone No. +49 89 2399 8712 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/10000

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-72 as originally filed

Claims, No.:

1-28 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/10000

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 20.

because:

☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28
	No:	Claims	

Inventive step (IS)	Yes:	Claims	1-28
	No:	Claims	

Industrial applicability (IA)	Yes:	Claims	1-19 and 21-28
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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/10000

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

ITEM III

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT). See also the paragraph on : "Industrial applicability" in item V below.

ITEM III ✓

Reference is made to the following documents:

- D1: WO 98 53817 A cited in the application
- D2: WO 98 53814 A cited in the application
- D3: WO 98 53818 A cited in the application
- D4: GB-A-1 201 121
- D5: US-A-4 105 602
- D6: WO 98 54207 A cited in the application
- D7: WO 97 03094 A cited in the application

NOVELTY (Article 33(2) PCT)

The present subject matter differs from D1 and D7 mainly on account of the carbamate group on position 4 of the present tyrosine residue.

The present subject matter differs from D2-D4 and D6 mainly on account of the present 2-aminopentanoyl residue.

The present subject matter differs from D5 mainly on account of the carbamate group on position 4 of the present tyrosine residue and of the present 2-aminopentanoyl residue.

The present subject matter fulfil therefore the requirements of Article 33(2) PCT.

INVENTIVE STEP (Article 33(3) PCT)

D1 is considered the closest prior art and discloses biarylalkanoic acids derivatives which are antagonists of VLA-4 and/or $\alpha_4\beta_7$, and are suitable for the treatment of inflammatory and autoimmune disorders. The present subject matter mainly differs from D1 on account of the present 4-carbamate tyrosine residue which replace the 4-(substituted)aryl phenylalanine residue in compounds of formula 1 according to claim 1 from D1 (see definition of R6 in claim 1 of D1 and compound **H** in scheme 3 on page 28 of D1. See also the definition of Y-R₁ in D1 and compare it with the present definition of R₃).

The problem to be solved by the present application is considered to be the provision of further VLA-4 and $\alpha_4\beta_7$ antagonists.

The problem has been solved, at least in vitro, as shown by the Pharmacological examples reported on pages 68-71 of present description.

None of the above mentioned prior art documents discloses the equivalence between 4-carbamate and 4-aryl residues, nor are other information provided by the said documents which would lead the skilled person to consider compounds of formula (I) according to present claim 1 as a solution for the aforementioned given problem. Thus, an inventive step can be acknowledged for the present subject matter (Article 33(3) PCT).

INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

For the assessment of the present claim 20 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

ITEM VIII

In claims 22-25, the subject matter is defined by functional expression, i. e. in terms of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/10000

a desired result (e. g. "... a group capable of forming a carboxylic acid ester") and do not fulfill therefore the requirements of Article 6 PCT.

PCT

REQUEST

The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No. **PCT/EP 99 / 10000**

International Filing Date

16 DEC 1999

(16.12.99)

EUROPEAN PATENT OFFICE

PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum) **PG3612/PCT**

Box No. I TITLE OF INVENTION	
Compounds useful in the treatment of inflammatory diseases	
Box No. II APPLICANT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below).	
Glaxo Group Limited Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN, GB	
<input type="checkbox"/> This person is also inventor.	
Telephone No. 0171 493 4060	
Facsimile No. 0181 966 8838	
Teleprinter No. 25456	
State (i.e. country) of nationality: GB	State (i.e. country) of residence: GB
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
ARMOUR, Duncan Robert Discovery Chemistry, IPC 924 Pfizer Limited Ramsgate Road Sandwich, Kent CT13 9NJ, GB	
This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (i.e. country) of nationality: GB	State (i.e. country) of residence: GB
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).	
TEUTEN, Andrew J. Glaxo Wellcome plc Glaxo Wellcome House, Berkeley Avenue Greenford, Middlesex UB6 0NN GB	
Telephone No.: 0171-493-4060 Facsimile No.: 0181-966-8838 Teleprinter No.: 25456	
Express Mail Label EL395942977US	
If no agent or common representative is/has been appointed and the space above is used instead to indicate to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BROWN, David
Roche Products Limited
Broadwater Road,
Welwyn Garden City
Hertfordshire
AL7 3AY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CONGREAVE, Miles Stuart
Glaxo Wellcome Cambridge Laboratory
University Chemical Laboratory
Lensfield Road
Cambridge
CB2 1EW, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

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all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

GORE, Paul Martin
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

GREEN, Darren Victor Steven
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

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all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HOLMAN, Stuart
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

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all designated States except the United States of America

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Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JACK, Torquil Iain Maclean
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

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the United States of America only

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the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KEELING, Steven Philip
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MASON, Andrew McMurtrie
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Sheet No. 4.....

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MORRISS, Karen
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

RAMSDEN, Nigel Grahame
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

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This person is applicant for the purposes of:

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all designated States except the United States of America

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the United States of America only

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the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WARD, Peter
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

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all designated States except the United States of America

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the United States of America only

☐

the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☐

the United States of America only

☐

the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line).....

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania..... | <input checked="" type="checkbox"/> LS Lesotho..... |
| <input checked="" type="checkbox"/> AM Armenia..... | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria..... | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia..... | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MD Republic of Moldova..... |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MG Madagascar..... |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BG Bulgaria..... | |
| <input checked="" type="checkbox"/> BR Brazil..... | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BY Belarus..... | <input checked="" type="checkbox"/> MW Malawi..... |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico..... |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CN China..... | <input checked="" type="checkbox"/> NZ New Zealand..... |
| <input checked="" type="checkbox"/> CU Cuba..... | <input checked="" type="checkbox"/> PL Poland..... |
| <input checked="" type="checkbox"/> CZ Czech Republic..... | <input checked="" type="checkbox"/> PT Portugal..... |
| <input checked="" type="checkbox"/> DE Germany..... | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark..... | <input checked="" type="checkbox"/> RU Russian Federation..... |
| <input checked="" type="checkbox"/> EE Estonia..... | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> ES Spain..... | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> FI Finland..... | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SI Slovenia..... |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SK Slovakia..... |
| <input checked="" type="checkbox"/> GE Georgia..... | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GH Ghana..... | <input checked="" type="checkbox"/> TJ Tajikistan..... |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TM Turkmenistan..... |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TR Turkey..... |
| <input checked="" type="checkbox"/> HU Hungary..... | <input checked="" type="checkbox"/> TT Trinidad and Tobago..... |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine..... |
| <input checked="" type="checkbox"/> IL Israel..... | <input checked="" type="checkbox"/> UG Uganda..... |
| <input checked="" type="checkbox"/> IN India..... | <input checked="" type="checkbox"/> US United States of America..... |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> UZ Uzbekistan..... |
| <input checked="" type="checkbox"/> JP Japan..... | <input checked="" type="checkbox"/> VN Viet Nam..... |
| <input checked="" type="checkbox"/> KE Kenya..... | <input checked="" type="checkbox"/> YU Yugoslavia..... |
| <input checked="" type="checkbox"/> KG Kyrgyzstan..... | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea..... | <input checked="" type="checkbox"/> ZW Zimbabwe |
| | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet. |
| <input checked="" type="checkbox"/> KR Republic of Korea..... | <input checked="" type="checkbox"/> CR Costa Rica..... |
| <input checked="" type="checkbox"/> KZ Kazakhstan..... | |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> DM Dominica..... |
| <input checked="" type="checkbox"/> LK Sri Lanka | <input checked="" type="checkbox"/> MA Morocco..... |
| | <input checked="" type="checkbox"/> TZ Tanzania..... |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Sheet No .6..

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box		
		Where earlier application is		
Filing Date of Earlier Application (day/month/year)	Number Of earlier application	national application: country	regional application:* regional Office	International application: receiving Office
item (1) (18.12.98) 18 December 1998	9828074.6	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): _____
 * Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rue 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) If two or more International Searching Authorities are competent to carry out the international search, indicate the authority chosen; the two-letter code may be used: ISA/	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional office)
--	---

Box. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets: request : 6 description (excluding sequence listing part) : 72 claims : 10 abstract : 1 drawings : sequence listing part of description : Total number of sheets : 89	This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):
--	--

Figure of the drawings which should accompany the abstract:	Language of filing of the International application: English
---	--

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



Andrew J. TEUTEN
Agent for the Applicants

For receiving Office use only		2. Drawings <input type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application: 16 DEC 1999 (16.12.99)	3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	5. International Searching Authority specified by the applicant: ISA/	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

Date of receipt of the record copy by the International Bureau

For International Bureau use only

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 August 2000 (17.08.00)	
International application No. PCT/EP99/10000	Applicant's or agent's file reference PG3612/PCT
International filing date (day/month/year) 16 December 1999 (16.12.99)	Priority date (day/month/year) 18 December 1998 (18.12.98)
Applicant ARMOUR, Duncan, Robert et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
23 June 2000 (23.06.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Charlotte ENGER Telephone No.: (41-22) 338.83.38
--	--

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

TEUTEN, Andrew, J.
Glaxo Wellcome plc
Glaxo Wellcome House, Berkeley
Avenue
Greenford
Middlesex UB6 0NN
ROYAUME-UNI

Date of mailing (day/month/year) 29 August 2000 (29.08.00)	Applicant's or agent's file reference PG3612/PCT
International application No. PCT/EP99/10000	International filing date (day/month/year) 16 December 1999 (16.12.99)

1. The following indications appeared on record concerning: <input checked="" type="checkbox"/> the applicant <input checked="" type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative		
Name and Address CONGREAVE, Miles, Stuart Glaxo Wellcome Cambridge Laboratory University Chemical Laboratory Lensfield Road Cambridge CB2 1EW United Kingdom	State of Nationality GB	State of Residence GB
Telephone No. _____		
Facsimile No. _____		
Teleprinter No. _____		
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input checked="" type="checkbox"/> the name <input type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence		
Name and Address CONGREVE, Miles, Stuart Glaxo Wellcome Cambridge Laboratory University Chemical Laboratory Lensfield Road Cambridge CB2 1EW United Kingdom	State of Nationality GB	State of Residence GB
Telephone No. _____		
Facsimile No. _____		
Teleprinter No. _____		
3. Further observations, if necessary: _____ _____ _____		
4. A copy of this notification has been sent to: <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority </div> <div> <input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other: _____ </div> </div>		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Catherine Massetti Telephone No.: (41-22) 338.83.38
--	---

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
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CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP 99/10000

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/58 C07D295/20 C07D307/91 C07D405/12 C07D307/66
 C07C271/40 C07K5/06 C07K17/08 C07K1/04 A61K31/325
 A61K31/445 A61K31/496 A61K31/5375 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 53817 A (MERK & CO., INC.) 3 December 1998 (1998-12-03) cited in the application schemes 1-5 claims 1,11,13; examples ---	1, 16, 18-21, 26-28
A	WO 98 53814 A (MERCK & CO., INC.) 3 December 1998 (1998-12-03) cited in the application scheme 1 claims 1,5,154,18-20; examples ---	1, 16, 18-21, 26-28
A	WO 98 53818 A (MERCK & CO., INC.) 3 December 1998 (1998-12-03) cited in the application claims 1,5,8-10 ---	1, 16, 18-20
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 March 2000

Date of mailing of the international search report

29/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

Int. Patent Application No

PCT/EP 99/10000

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 201 121 A (FARBWERKE HOECHST AG) 5 August 1970 (1970-08-05) claims 1,4,5,7; examples ----	1,16, 22-25
A	US 4 105 602 A (R. L. COLESCOTT ET AL.) 8 August 1978 (1978-08-08) column 2, line 26 - line 37 columns 3 and 4, bottom of page, coupling reaction; columns 5 and 6, top of page, coupling reaction ----	26-28
A	WO 98 54207 A (CELLTECH THERAPEUTICS LTD.) 3 December 1998 (1998-12-03) cited in the application ----	
A	WO 97 03094 A (BIOGEN, INC.) 30 January 1997 (1997-01-30) cited in the application -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/10000

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 20
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/10000

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9853817	A	03-12-1998	AU	7703198 A	30-12-1998
WO 9853814	A	03-12-1998	NONE		
WO 9853818	A	03-12-1998	AU	7703298 A	30-12-1998
GB 1201121	A	05-08-1970	CH	496668 A	30-09-1970
			DE	1593858 A	29-10-1970
			DE	1643327 A	27-05-1971
			NL	6802947 A	03-09-1968
			US	3538070 A	03-11-1970
US 4105602	A	08-08-1978	NONE		
WO 9854207	A	03-12-1998	AU	7667498 A	30-12-1998
			EP	0984981 A	15-03-2000
WO 9703094	A	30-01-1997	AU	716276 B	24-02-2000
			AU	6489496 A	10-02-1997
			BG	102241 A	30-12-1998
			BR	9609782 A	09-03-1999
			CA	2226868 A	30-01-1997
			CN	1193325 A	16-09-1998
			CZ	9800052 A	15-04-1998
			EP	0842196 A	20-05-1998
			FI	980033 A	05-03-1998
			HU	9802202 A	28-01-1999
			JP	11511124 T	28-09-1999
			NO	980097 A	11-03-1998
			PL	324491 A	25-05-1998
			SK	3798 A	08-07-1998